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NQO1 C609T polymorphism in distinct entities of pediatric hematologic neoplasms

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A B S T R A C T

Background and Objectives. NAD(P)H:quinone oxidoreductase 1 (NQO1) is an enzyme that protects cells against mutagenicity from free radicals and toxic oxygen metabolites. The gene coding for NQO1 is subject to a genetic polymorphism at nucleotide position 609 (C→T) of the human NQO1 cDNA. Heterozygous individuals (C/T) have intermediate activity and homozygotes for the variant allele (T/T) are deficient in NQO1 activity. In previous studies, genotypes conferring lower NQO1 activity have been associated with an increased risk of acute leukemia, particularly infant leukemia carrying *MLL/AF4* fusion genes. In the present study, we investigated this association in our population and extended the analysis to other subgroups of pediatric hematologic neoplasms characterized by specific fusion genes.

Design and Methods. We genotyped 138 patients with childhood acute lymphoblastic leukemia (ALL) carrying distinct fusion genes (*MLL/AF4*=35; *BCR/ABL*=31; *TEL/AML1*=72), 71 cases of pediatric sporadic Burkitt's lymphoma and 190 healthy control individuals for the NQO1 C609T polymorphism.

Results: When compared to the healthy control group, only children with Burkitt's lymphoma significantly more often had *NQO1* genotypes associated with lower NQO1 activity (odds ratio, 1.81; p=0.036), predominantly at a younger age (< 9 years at diagnosis: odds ratio, 3.02; p=0.003).

Interpretation and Conclusions. Our results suggest that in our population the NQO1 C609T polymorphism does not confer an increased risk of the investigated entities of childhood ALL. However, there may be a modulating role for NQO1 in the pathogenesis of pediatric sporadic Burkitt's lymphoma.

Key words: childhood ALL, Burkitt's lymphoma, NQO1, polymorphism, chromosomal translocation.

The detoxification enzyme NAD(P)H: quinone oxidoreductase 1 (NQO1), also known as DT-diaphorase, is an obligate two-electron reductase that is expressed in a broad range of tissues in the human body, including the epithelium of various organs, vascular endothelium and nerve tissue.[1-3] NQO1 protects cells against mutagenicity from free radicals and toxic oxygen metabolites generated by the one-electron reductions catalyzed by cytochromes P450 and other enzymes[4]. Substrates for the enzyme include quinones, quinone imines, and azo-dyes. In addition, it was recently shown that NQO1 has a direct role in the protection against oxidative stress.[5]

The gene coding for NQO1 is subject to polymorphism (C609T) with a C→T base change at position 609 of the human NQO1 cDNA, leading to a change in the amino acid sequence of the protein (P187S).[6,7] Heterozygous individuals (C/T or NQO1*1/*2) have intermediate activity and homozygotes for the variant allele (T/T or NQO1*2/*2) are deficient in NQO1 activity.[8,9] In previous studies, the *NQO1* C609T polymorphism was associated with risk of childhood and adult acute lymphoblastic leukemia (ALL) as well as *de novo* and therapy-associated acute myeloid leukemia (AML).[10-16] Inconsistent results have been reported for solid malignancies (e.g., gastrointestinal tract, breast and lung cancer).[17-23] Particularly strong associations have been reported for infant leukemias with chromosomal translocations involving the *MLL* gene on chromosome band 11q23, especially those carrying a t(4;11) where the *MLL* gene is fused to the *AF4* gene on chromosome band 4q21.[12,15] To analyze this association in our population and to investigate potential associations of NQO1 deficiency

with additional entities of hematologic malignancies characterized by specific genetic aberrations, we genotyped 35 *MLL/AF4*-positive (+), 31 *BCR/ABL*+, and 72 *TEL/AML1*+ childhood ALL patients, 71 patients with pediatric sporadic Burkitt's lymphoma, and 190 healthy control individuals for the *NQO1* C609T polymorphism.

Design and Methods

Patients and controls

Samples from patients diagnosed with *de novo* ALL from October 1986 to December 2000 were collected through the International Berlin-Frankfurt-Münster Study Group (I-BFM-SG) from German, Austrian and Czech study centers.[24,25] The patients with Burkitt's lymphoma had been included in the German-Austrian-Swiss NHL-BFM 86 and NHL-BFM 90 therapy trials on non-Hodgkin's lymphoma (NHL) of childhood and adolescence.[26,27] For ALL, the diagnosis was established in the respective central reference laboratory by morphological FAB criteria and cytochemistry when there were at least 25% lymphoblasts in the bone marrow, or blasts in the peripheral blood. The immunophenotype and positivity for *TEL/AML1*, *BCR/ABL*, and *MLL/AF4* fusion transcripts were assessed as described previously.[28-31] The cases of NHL were classified as Burkitt's lymphoma according to the criteria of the updated Kiel and the World Health Organization classification.[32,33] Tumor slides of all patients were reviewed by central reference pathologists. Cytogenetic data for Burkitt's lymphoma patients were not available. Staging was based on the criteria of the St. Jude staging system for pediatric lymphoma.[34] Controls consisted of blood samples from healthy blood donors [18-68 years of age, 130 males (68.4%) and 60 females (31.4%)], with no history of malignant neoplastic disease. These controls were collected through the Department of Transfusion Medicine, Hannover Medical School, Germany. All individuals included in the present study were of Caucasian descent. Informed consent was obtained from patients' parents or legal guardians and control individuals. The study was approved by the local ethics committee of the Hannover Medical School.

Genotyping

DNA was extracted from either leukemic (ALL) or tumor-free bone marrow smears (Burkitt's lymphoma) and whole blood (controls) using the High Pure PCR Template Preparation Kit (Roche Diagnostics, Mannheim, Germany). *NQO1* C609T genotyping was performed as previously described.[11]

Statistical analysis

The association of *NQO1* C609T genotype with risk of chromosomal translocation/disease was examined by unconditional logistic regression analysis to calculate odds ratios (OR) and their 95% confidence intervals (CI). p values of < 0.05 were considered statistically significant. Genotype was used as a categorical variable in these analyses. The expected frequency of control genotypes was analyzed by the Hardy-Weinberg equilibrium test. The SPSS statistical package (SPSS Inc., Chicago, IL, USA) was used for computerized calculations.

Results

In the present study, 399 Caucasian individuals (190 control subjects, 209 patients) were genotyped for the *NQO1* C609T polymorphism. The characteristics of the patients divided by diagnostic entity are shown in Table 1. Genotype frequencies among controls were in Hardy-Weinberg equilibrium (p=0.81). The genotype distribution in controls and in the investigated entities of pediatric hematologic neoplasms as well as associations with risk of chromosomal translocation/disease are shown in Table 2. When compared to the healthy control group, only patients with Burkitt's lymphoma significantly more often displayed NQO1 genotypes associated with lower NQO1 activity ($p\,\chi^2$=0.036). This effect was predominant in younger Burkitt's patients who carried a NQO1*2 allele significantly more often than did their older counterparts ($p\,\chi^2$=0.029; split at the rounded median of 9 years of age at diagnosis; Table 2). No statistically significant difference with regard to age distribution was observed in the other entities analyzed in our study. No differences in genotype distributions within controls or the investigated entities of pediatric hematologic neoplasms were observed with regard to gender. Of interest, in the largest set of patients reported so far, we were not able to confirm the previously published association of low-activity NQO1 genotypes and risk of a t(4;11) or *MLL/AF4* rearrangement.[12,15] Even when restricting the analysis to t(4;11) or *MLL/AF4*+ patients younger than 18 months at diagnosis, as investigated by Wiemels *et al.*,[12] no significant associations were observed (Table 2).

Discussion

This is the first study to demonstrate an association of *NQO1* C609T genotype with pediatric sporadic Burkitt's lymphoma. However, with regard to *MLL/AF4*+ ALL, our results are in contrast to those of two previous reports demonstrating particularly strong associ-

Table 1. Patients' characteristics by diagnostic entity.

	MLL/AF4+ *n = 35*	*BCR/ABL+* *n = 31*	*TEL/AML1+* *n = 72*	*Burkitt's* *n = 71*
	Number of subjects (%)			
Gender[a]				
Male	19 (54.3)	20 (64.5)	39 (54.2)	57 (80.3)
Female	16 (45.7)	11 (35.5)	33 (45.8)	14 (19.7)
Age at diagnosis (y)[b,c]				
≤ 1	20 (57.1)	–	–	–
> 1-10	8 (22.9)	17 (54.8)	63 (87.5)	44 (62.0)
> 10-15	6 (17.1)	11 (35.5)	8 (11.1)	22 (31.0)
> 15-19	1 (2.9)	3 (9.7)	1 (1.4)	5 (7.0)
Initial WBC ($10^3/\mu L$)				
< 50	6 (17.1)	13 (41.9)	65 (90.3)	71 (100)
50 - 100	6 (17.1)	4 (12.9)	5 (6.9)	–
> 100	23 (65.7)	14 (54.2)	2 (2.8)	–
Stage (St. Jude classification)[d]				
I	–	–	–	11 (15.5)
II	–	–	–	21 (29.6)
III	–	–	–	32 (45.1)
IV	–	–	–	7 (9.9)
Immunophenotype				
Pro-B	25 (71.4)	-	2 (2.8)	–
Pre-B	1 (2.9)	6 (19.4)	8 (11.1)	–
Common	9 (25.7)	24 (77.4)	60 (83.3)	–
Mature B	–	–	–	71 (100)
B, not further specified	–	–	1 (1.4)	–
T	–	1 (3.2)	–	–
Hybrid	–	–	1 (1.4)	–

[a]total patient sample: 64.6% male, 35.4%female; [b]y: years; [c]median age: MLL/AF4 = 0.77 y, BCR/ABL: 8.33 y, TEL/AML1: 4.21 y, Burkitt's lymphoma: 8.55 y; [d]see reference [34].

ations of low *NQO1* activity genotypes with a t(4;11) or *MLL/AF4* rearrangement.[12,15] There are different explanations for these contrasting results. First, the present study included patients from Central Europe (Austria, Czech Republic, Germany) while the above mentioned studies were carried out in the United Kingdom and the United States. It can be expected from the literature that *NQO1* genotype frequencies in Caucasians are relatively similar. Our controls show the same *NQO1* C609T genotype distribution as the control group in the work by Wiemels *et al.*[12] However, it is possible that there are differences between countries with regard to specific exposure histories for leukemia cases. Furthermore, we cannot assess the potential influence of any gene-gene or additional gene-environment interactions that may differ between the investigated populations. Secondly, considering the potential importance of parental genotype with respect to an *in utero* pathogenesis of a *MLL/AF4* rearrangement, our results may simply reflect passage of the *NQO1*1* allele from heterozygous parents to their offspring with *MLL/AF4*+ leukemia. Thirdly, selection bias is an issue in every case-control approach and certainly may have had an effect on our results, as well. Nevertheless, the characteristics and treatment outcome of the patients investigated in the present study did not significantly differ from the respective study populations they were recruited from (*data not shown*). Finally, as far concerns previous investigations, our results may simply be due to chance and the small numbers of patients. Thus, the results presented in this study should be interpreted with the necessary caution and need to be confirmed in future investigations. An important perspective for association studies that may help to resolve problems related to the current practice of performing association analysis at the SNP or the haplotype level, was recently published by Neale and Sham.[35] They suggested a move towards a gene-based approach in which all variants within a putative gene are considered jointly to facilitate the resolution of inconsistencies arising from differences between populations. One require-

Table 2. Distribution of *NQO1* C609T genotype and its association with risk of chromosomal translocation/disease.

	NQO1	*Number of subjects (%)*	*Odds ratio[a] (CI[b])*	*p*
Controls				
(n=190)	*1/*1	126 (66.3)	–	–
	*1/*2	61 (32.1)	–	–
	*2/*2	3 (1.6)	–	–
MLL/AF4+				
(n=35)	*1/*1	25 (71.4)	1.00[c]	
	*1/*2	9 (25.7)	0.79 (0.36 - 1.74)	0.56
	*2/*2	1 (2.9)		
MLL/AF4+				
< 18 mo at diagnosis[d]	*1/*1	18 (81.8)	1.00[c]	
(n=22)	*1/*2	4 (18.2)	0.44 (0.14-1.35)	0.15
	*2/*2	-		
TEL/AML1+				
(n=72)	*1/*1	49 (68.1)	1.00[c]	
	*1/*2	21 (29.2)	0.92 (0.52-1.65)	0.79
	*2/*2	2 (2.8)		
BCR/ABL+				
(n=31)	*1/*1	18 (58.1)	1.00[c]	
	*1/*2	12 (38.7)	1.42 (0.38-3.78)	0.37
	*2/*2	1 (3.2)		
Burkitt's lymphoma				
(n=71)	*1/*1	37 (52.1)	1.00[c]	
	*1/*2	29 (40.8)	1.81 (1.04-3.15)	0.036
	*2/*2	5 (7.0)		
Burkitt's lymphoma				
≤ 9 y at diagnosis[e]	*1/*1	15 (39.5)	1.00[c]	
(n=38)	*1/*2	21 (55.3)	3.02 (1.47-6.18)	0.003
	*2/*2	2 (5.3)		

*[a]compared to healthy controls; individuals heterozygous or homozygous for NQO*2 were combined into one category; [b]confidence interval; [c]reference category; [d]patients < 18 month at diagnosis, as investigated by Wiemels et al.;[12] [e]divided at rounded median age of diagnosis.*

ment for a chromosomal translocation is the occurrence of DNA double-stranded breaks in the respective partner loci at the same time.[36,37] The *MLL* gene at chromosome band 11q23 is frequently involved in chromosomal rearrangements in acute leukemias and the *c-myc* gene at chromosome band 8q24 is rearranged in Burkitt's lymphoma.[38,39] It has been shown for both genes, *MLL* and *c-myc*, that apoptosis-inducing substances can induce double-stranded breaks in DNA within the breakpoint cluster regions.[40,41] As an additional requirement for chromosomal translocation upon generation of DNA double-strand breaks, it is necessary for the respective cells to survive this genetic damage. With regard to this issue, differences in the sensitivity of cells to undergo apoptosis upon acquiring DNA double-stranded breaks have been suggested to play a role in the pathogenesis of chromosomal translocations.[42,43] Intriguingly, NQO1 was shown to sensitize cells to undergo apoptosis by tumor necrosis factor-α and, more recently, it was shown that wild-type NQO1 stabilized wild-type p53 whereas the NQO1*2 coded inactive NQO1 did not.[44,45] Asher *et al.* suggested that exposure towards carcinogenic substrates of NQO1 could lead to increased genotoxic damage at lower p53 levels in individuals with lower NQO1 activity than in wild-type NQO1 individuals.[45] As accumulation of p53 is important for growth arrest and induction of apoptosis, lower NQO1 activity upon carcinogenic exposure may, therefore, confer a higher susceptibility to accumulation of genetic mutations (e.g., chromosomal translocations) in hematopoietic precursor cells and finally lead to neoplastic disease.

NQO1 genotype frequencies differ significantly between different ethnic groups, with the *NQO1*2* allele being reported to be approximately twice as common in Asian and Hispanic populations (allele frequencies 0.45 and 0.39, respectively).[4,46] Of interest, children of Asian ethnic origin in Britain have consistently been found to have a higher incidence of leukemias and lymphomas, particularly lymphomas in

early childhood (0-4 years of age), and children of Hispanic origin have been reported to have higher incidences of ALL and lymphomas in the USA.[47-49] However, the lack of information on potential lifestyle-specific environmental exposures and incidence rates of well characterized molecular subgroups in different populations makes it difficult to speculate on a potential role for NQO1 deficiency in association with the above mentioned obervations. Of interest, with regard to environmental exposure and molecularly defined leukemia subgroups, a case-control study by Alexander and colleagues identified, for example, carbamate-based insecticides as a risk factor for *MLL*-rearranged infant leukemias.[50] Although no specific substances were identified, exposure to pesticides has been repeatedly identified as a risk factor, also for pediatric Burkitt's lymphoma.[51,52] A potential link between exposure to pesticides and NQO1 could be that NQO1 has a direct role in the protection against oxidative stress and pesticides induce oxidative stress as one mechanism of their toxic action.[5,53] Another important observation is that pesticides are potent inducers of NQO1 in rat livers.[54] The different results for *MLL/AF4*$^+$ ALL and NQO1 deficiency that we and others observed are not necessarily contradictory. They may point towards potential differences in exposure between different populations and could be useful in elucidating the etiology of chromosomal translocation/disease when incorporated in well-designed molecular epidemiologic studies. In conclusion, we suggest a common exposure (e.g., pesticides) with its effects modulated through NQO1 is associated with risk of different hematologic neoplasms.

While all authors fulfill the requirements for authorship, more specifically OAH, JT, AR, MS, RR, RM, AB, KW and MS had the major input designing the study and were involved in the interpretation of the results. TK, MM, SS, JH, SV and H-AE were mostly involved in acquisition of available preserved samples or bone marrow smears, DNA isolation, and genotyping, and the acquisition of data, as well as the recruitment of control individuals.

This study was conducted under the umbrella of the I-BFM-SG.

TK, TL, GC and MS were involved in the statistical analysis. MS and TK wrote the first draft of the paper, which was critically revised by all other authors to derive the final version of the paper. All authors approved the final version of the paper. The authors reported no potential conflicts of interest.

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